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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Wai C. Wong, et al.	
U.S. Serial No.	: 09/933,106	Group Art Unit: 1624
Filed	: August 20, 2001	Examiner: V.Balasubramanian
For	: IMIDAZOLE AND IMIDAZOLINE DERIVATIVES AND USES THEREOF	

1185 Avenue of the Americas
New York, New York 10036

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF WAI WONG, YOON JEON, T.G. MURALI DHAR AND CHARLES GLUCHOWSKI UNDER 37 C.F.R. §1.131

We, Wai Wong, Yoon Jeon, T.G. Murali Dhar and Charles Gluchowski, hereby declare as follows:

1. Prior to November 11, 1996, we conceived of in the United States and demonstrated in rhesus monkeys that alpha 2 agonists have analgesic activity and thus utility as analgesics. Its evidence of this conception we have attached hereto as **Exhibit A**, a copy of an agenda for a meeting of the alpha agonist project team: The date of the meeting has been redacted but was prior to January 31, 1995.

2. Prior to November 11, 1996, we also conceived of the subject invention claimed in the above-identified patent application in the United States. Specifically we conceived of the genus of compounds recited in pending claim 1, the text of which is attached hereto as **Exhibit 1**, in the United States prior to

November 11, 1996. As evidence of our conception we have attached hereto true copies of 2 consecutive pages from the notebook of one of us, Wai Wong, which document our conception of the claimed compounds as alpha 2 adrenoreceptor selective compounds, i.e. compounds in furtherance of our conception then having utility based on analgesic activity. Although the specific dates on these pages have been redacted they are prior to November 11, 1996.

3. Prior to November 11, 1996, one of us, Wai Wong, actually made specific compounds encompassed within the scope of the claim 1 in the United States. In particular, the compound of example 10 of the application was made in the United States prior to November 11, 1996. A true copy of a notebook page describing the synthesis of the compound of example 10 is attached hereto as Exhibit B. The date of this notebook page is prior to November 11, 1996 but has been redacted.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10/29/03
Date

W C Wong
Wai Wong

November 11, 1996. As evidence of our conception we have attached hereto true copies of 2 consecutive pages from the notebook of one of us, Wai Wong, which document our conception of the claimed compounds as alpha 2 adrenoraceptor selective compounds, i.e. compounds in furtherance of our conception then having utility based on analgesic activity. Although the specific dates on these pages have been redacted they are prior to November 11, 1996.

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29 October 2003
Date

T.G. Murali Dhar

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10/30/2003
Date

John Deon

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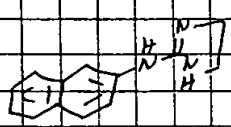
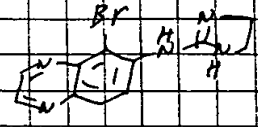
10/3/03
Date

Charles Gluchowski
Charles Gluchowski

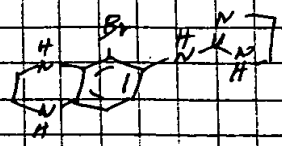
From Page No.



SNAP 5094

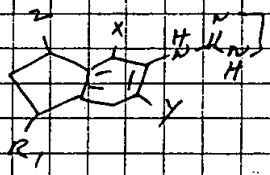


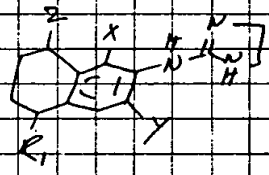
SNAP 1019

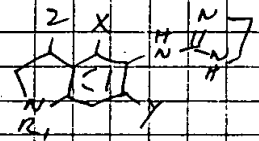


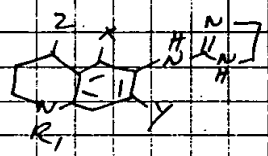
SNAP 1085

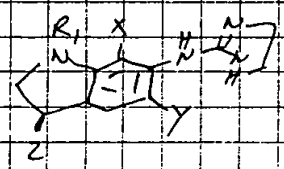
Since SNAP 5094 is selective for the A_{2c} receptor which is our target receptor, and since SNAP 1085 is more selective than SNAP 1019, the following compounds are proposed as analogs of SNAP 5094 which are expected to show even better selectivity than SNAP 5094.

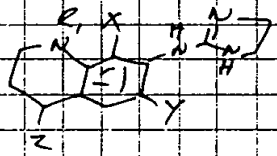












To Page No.

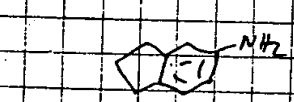
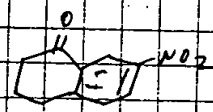
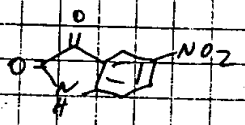
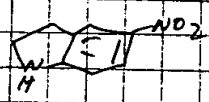
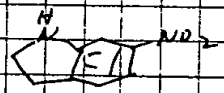
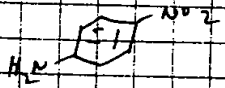
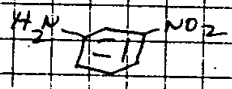
Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by W C Wong	

Project No._____
Book No._____ TITLE _____

From Page No.___

Where X, Y = H, halogen, alkyl, alkoxy, nitro, CN;
Z = H, alkyl, alkoxy;
R_1 = H, alkyl

The following are envisioned to be starting materials for the target compounds.

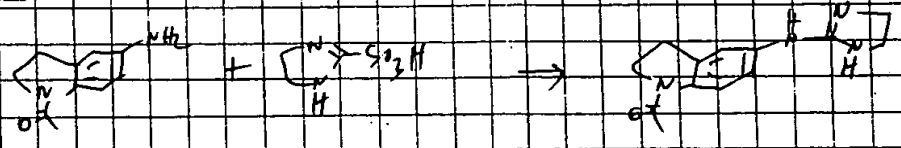








To Page No.____

Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by WC Wong	

From Page No.

6-4-93



MW 176.22 MW 150.16 MW 244.30

3904-49-1 (207 mg, 1.17 mmol) was mixed with 2-imidazolinesulfonic acid (349 mg, 2.32 mmol) in t-butyl alcohol (8 mL) which was then heated at reflux overnight (two nights). Tlc (EtOAc / MeOH / Et_3N, 5:2:0.2) showed almost complete reaction. Hence the solvent was evaporated to give a light brown oil. It was dissolved in EtOAc / MeOH / Et_3N (25:15:2) + flash chromatographed over silica gel (15 g) eluting with the same solvent to give a light brown foam (3904-81-1, 337 mg). EtOH did not dissolve everything, so it was filtered and then triturated with EtOAc. Refrigeration gave a white solid (3904-81-2, 164 mg).

Anal. calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93
Found: C, 51.26; H, 6.10; N, 18.47; S, 1.89.

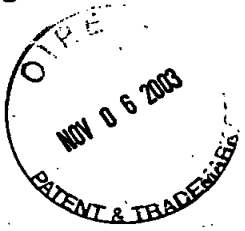
The residue from 3904-81-2 was dissolved in EtOAc / MeOH / Et_3N (10:2:0.6) + flash chromatographed over silica gel (6g) eluting with the same solvent to give a yellow solid (82 mg, 3904-81-3). 9% was dissolved in MeOH / EtOH and treated with fumaric acid (38 mg) in EtOH. Upon standing, a light brown crystal was obtained (3904-81-4, 67 mg).

Anal. calcd for $C_{13}H_{16}N_4O \cdot C_4H_4O_4$: C, 56.66; H 5.59; N, 15.55.
MW 360.37
Found: C, 56.39; H, 5.40; N, 15.38. mp 200-203 °C (dec).
SNAP 5352 ^{1}HNMR (CD_3OD).

To Page No.

Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by WC Wong	

ALPHA AGONIST PROJECT TEAM MEETING



3:00 PM
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AGENDA

Introduction - C. Gluchowski

Alpha 2 Agonists - Analgesia

1. Analgesic effects of SNAP alpha 2 agonists in rhesus monkeys - C. Forray

Alpha Agonists - Urinary Incontinence

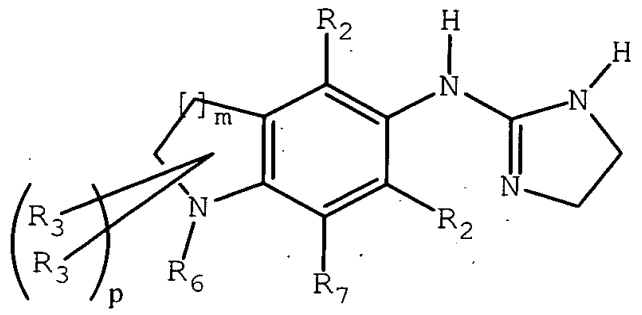
1. Background and rationale - W. Heydorn
2. Pharmacology update and future plans:

   Cloned receptors, tissue and *in vivo* studies - C. Forray, D. Craig
   Localization - E. Gustafson

3. Chemistry update and future plans - D. Dhanoa
4. Discussion - All

Reminder: The presentations and handouts should be in a format which covers the following points: objective, rationale, previous results, current results, conclusions and future plans. Please make sure that all data that are presented in overhead form are included in your handouts.

Claim 1 A compound having the structure:



wherein each R_2 is independently H; F; Cl; Br; I; $-NO_2$, $-CN$; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-OH$; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_3 is independently H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-(CH_2)_qOH$; $-OH$; $=N-OR_4$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_4 is independently H; straight chained or branched C_1-C_4 alkyl, C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; or phenyl;

wherein R_6 is H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-CH_2CH_2(CH_2)_qOH$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein R_7 is independently H; -CN; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; -OH; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein m is 1 or 2;

wherein each p is independently 0, 1 or 2; and

wherein each q is independently 0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.